REMARKS

Claims 1 to 57 are pending. Claims 6, 7, 11-48, 50-52, and 54 have been withdrawn from consideration. Consequently, claims 1-5, 8-10, 49, 53, and 55-57 are under consideration.

Claims 1, 3-5, 8-10, 49, 55, and 56 are amended.

Amendments to the Specification

The specification has been amended to update citation information for patent applications cited in Applicants' disclosure.

Amendments to the Claims

Claim 1 is amended as requested in the Office Action to define in the claims the first use of the acronym TLR. The amendment is fully supported by the specification at, for example, page 1, line 16.

Claims 1 and 49 are amended to recite particular TNF/R agonists. This amendment is fully supported throughout Applicants' disclosure such as at, for example, page 12, lines 11-21 and Examples 1-11 at pages 26-30.

Claims 1 and 49 also are amended to recite that the immunostimulatory combination produces a synergistic increase in the immune response induced in the subject. This amendment is fully supported throughout Applicants' disclosure such as at, for example, page 6, lines 13-18; page 5, lines 9-11; and Examples 1-11 at pages 26-30.

Claim 3 is amended as requested in the Office Action to define in the claims the first use of the acronym IRM. The amendment is fully supported by the specification at, for example, page 1, lines 14-15.

Claim 4 is amended to recite an additional TLR agonist. This amendment is fully supported by the specification at, for example, page 24, lines 5-7 and Example 11 at page 29, line 26 through page 30, line 4.

Claim 5 is amended to recite particular classes of compounds that may be useful as the TLR agonist. This amendment is fully supported by Applicants' disclosure such as at, for example, page 10, line 13 through page 11, line 25.

Claims 8 and 55 are amended to recite that the 4-1BB agonist comprises an agonistic antibody. This amendment is fully supported by Applicants' disclosure at, for example, page 12, lines 11-21, and Example 9 at page 29, lines 5-11.

Claim 9 is amended to recite particular CD40 agonists. This amendment is fully supported by Applicants' disclosure at, for example, page 12, lines 11-21, and Examples 1-11 at pages 26-30.

Claims 10 and 56 are amended to recite that the CD40 agonist comprises an agonistic antibody. This amendment is fully supported by Applicants' disclosure at, for example, page 12, lines 11-21, and Examples 1-11 at pages 26-30.

No new matter is introduced by any of these amendments.

Interview Summary

Applicants thank Examiner Kaufman for the courtesy of a telephonic interview conducted January 9, 2007. Participating in the interview on behalf of Applicants were Applicants' undersigned representative Christopher Gram, inventor Dr. Ross M. Kedl, and Dr. Kedl's legal counsel Robin Teskin.

The parties discussed the scope enabled by Applicants' disclosure, particularly with respect to TLR agonists and TNF/R agonists. The specifics of Applicants' remarks are summarized below.

§ 112 Rejections

Claims 1-5, 8-10, 49, 53, and 55-57 stand rejected under the enablement requirement of 35 USC § 112, first paragraph. Of the rejected claims, claims 1 and 49 are the only independent claims. Consequently, the remarks that follow are limited to the independent claims, but are equally applicable to all claims that depend, directly or indirectly, from claim 1 or claim 49.

The Office Action states that Applicants' disclosure fails to enable one skilled in the art to make and/or use the invention commensurate with the scope of the claims, particularly with respect to the terms "TLR agonist" and "TNF/R agonist."

The claims have been amended to recite particular classes of TNF/R agonists, namely, CD40 agonists and/or 4-1BB agonists. Applicants submit the disclosure fully enables one skilled

in the art to make and/or use the claimed invention with respect to CD40 agonists and 4-1BB agonists.

Applicants submit that the disclosure also fully enables one skilled in the art to make and/or use the claimed invention across the full scope of TLR agonists. In the telephonic interview of January 9, 2007, Dr. Kedl supported Applicants position with commentary that is summarized as follows:

Initial experimentation using both CD40 agonists and TLR7 agonists revealed a surprising synergy between the two pathways. That is, the combined administration of TLR7 agonists and CD40 agonists resulted in the expansion of CD8+ T cells that was exponentially greater than the expansion of T cells observed after administration of either agonist alone. While one might expect additive properties between two known immune stimuli (i.e., a two-fold increase in the T cell response), the results obtained were truly synergistic (e.g., a 10- to 20-fold increase in the T cell response) and thus highly unexpected.

The TLRs are stimulated by a diverse spectrum of molecules derived from microbial and/or viral agents. While ligands or agonists of some of the TLRs can be made synthetically, most human TLRs have known natural agonists or ligands derived from known viruses or microbes. Some example natural TLR agonists are:

TLR1	Bacterial lipopeptides, Pam3cys
TLR2	Lipoproteins, zymosan, MALP-2, Pam3cys
TLR3	Double-stranded virus RNA
TLR4	Lipopolysaccharide (LPS) of Gram-negative bacteria
TLR5	Bacterial flagellins
TLR6	MALP-2, zymosan
TLR7	Single-stranded RNA from RNA viruses
TLR8	Single-stranded RNA from RNA viruses
TLR9	Viral and bacterial CpG-containing DNA

Although the molecular family of TLR ligands is indeed diverse, the signaling pathways downstream of any given TLR are quite similar, having common molecular intermediates shared between all TLRs (e.g., MyD88, TRIF). The inventors therefore speculated that synergy with CD40 might be a property of TLR stimulation in general, and not limited to stimulation of TLR7. Upon further experimentation, the inventors determined that this was indeed the case; that

immunization with any agonist of any of the known TLRs, in combination with the CD40 agonist, resulted in a CD8+ T cell response that was synergistically—and often even exponentially—greater than response following immunization with either stimulus alone. This principle was true for representative agonists of TLR 1/2 (Pam3cys), 2/6 (MALP-2), TLR3 (PolyIC), TLR4 (LPS, MPL), TLR5 (flagellin), TLR9 (CpG 1826), and of course TLR7 (imidazoquinolines). These represent both natural (Pam3cys, MALP-2, LPS, MPL, flagellin) and synthetic (polyIC, CpG, imidazoquinolines) TLR stimuli. All of these TLR stimuli are exemplified in the original application except flagellin (TLR5). Flagellins are, however, described as possible TLR agonists in the original application (page 7, line 16). Because the signaling pathway downstream of TLR5 is similar to the other TLRs exemplified in the application, there was no reason to suspect that synergy would not be observed with immunization with both a TLR5 agonist and a CD40 agonist. In subsequent experiments, synergy between TLR5 and CD40 was indeed shown.

The only TLR that lacks experimental proof of synergy with CD40 is TLR10, for which there are no known agonists. TLR10 has been shown, however, to be functional and share with the other TLRs signaling through a MyD88-dependent pathway. (Hasan *et al.*, *J. Immunol.* (2005), 174:2942-2950.) Given the demonstration of the universal synergy between TLR1-9 and CD40, and particularly in light of the fulfilled expectation of synergy between TLR5 and CD40, there is no reason to expect anything other than synergy between TLR10 and CD40.

Therefore, every TLR agonist tried so far synergizes with CD40 stimulation for the induction of potent CD8+ T cell immunity. CD40 is a member of the TNFR/L super family and a number of other family members have stimulatory capacity, to one degree or another, for the induction of cellular immunity. The inventors therefore speculated that if synergy with CD40 is a general property of the TLRs, then perhaps synergy with the TLRs is a general property of the TNF receptors. In examining another representative of the TNF receptor family, 4-1BB, the inventors found the results consistent with this hypothesis; namely that the combined administration of 4-1BB and TLR agonists generated a CD8+ T cell response synergistically larger than administration of either stimulus alone (See Example 9). Thus, the comments made above with regard to synergy between TLR agonists and CD40 agonists apply equally to the combination of TLR agonists and 4-1BB agonists.

Applicants submit that, in light of Dr. Kedl's commentary summarized above, the full scope of the claims with respect to TLR agonists is enabled.

Therefore, Applicants submit that the full scope of the claims, as amended herein, is enabled. Applicants have provided working examples demonstrating synergy using agonists of eight of the ten known human TLRs in combination with a CD40 agonist and/or a 4-1BB agonist. Subsequent work has generated data confirming synergy using an agonist of a ninth TLR. Moreover, Applicants have provided methods for determining whether a particular compound is an agonist of any particular TLR (see, e.g., page 8, line 4 through page 9, line 7).

In summary, Applicants submit that claims 1-5, 8-10, 49, 53, and 55-57, as amended herein, are patentable under 35 USC § 112, first paragraph, and respectfully ask that the rejection be withdrawn.

§ 103 Rejections

Claims 1-5, 8-10, 49, 53, and 57-59 stand rejected under 35 USC § 103(a) as being unpatentable over Ito *et al.* or Hemmi *et al.* in view of Melief *et al.*

Specifically, Ito *et al.* and Hemmi *et al.* are said to teach that certain TLR7 agonists have immunostimulatory activity. The Office action acknowledges that these references do not teach or suggest the combination of a TLR7 agonist and a CD40 agonist. Melief is said to teach that a certain CD40 agonist possesses certain immunomodulatory activity. The Office Action states that it would have been obvious for one skilled in the art to combine the immunostimulatory activities of a TLR7 agonist and a CD40 agonist.

The claims have been amended to recite that the combination of a TLR agonist and either a CD40 agonist or a 4-1BB agonist produces a synergistic immune response when administered to a subject. This surprising result is neither taught nor suggested in the references cited in the Office Action.

Therefore, Applicants submit that claims 1-5, 8-10, 49, 53, and 57-59, as amended herein, are patentable under 35 USC § 103(a) over Ito *et al.* or Hemmi *et al.* in view of Melief *et al.* Applicants respectfully ask, therefore, that the rejection under 35 USC § 103(a) as be withdrawn.

CONCLUSION

In view of the above, it is submitted that the application is in condition for allowance. Reconsideration of the application is requested.

Allowance of claims 1-5, 8-10, 49, 53, and 57-59, as amended, at an early date is solicited.

Respectfully submitted,

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